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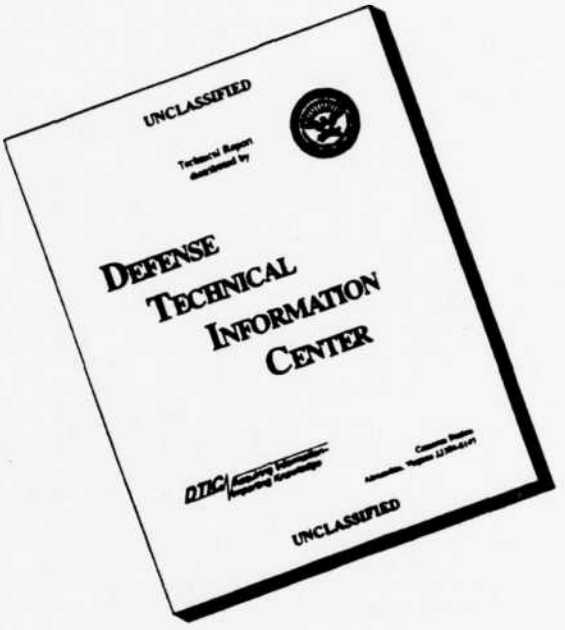

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PRINCIPAL INVESTIGATOR: James R. Piper

CONTRACTING ORGANIZATION: Southern Research Institute
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The goal of the proposed research is to provide prophylaxis against cyanide through its sequestration by covalent bond formation. Three strategies were pursued: (1) sulfur-rich compounds which could serve as sulfane sulfur donors to rhodanese and other sulfur transferases; (2) compounds containing multiple carbonyl moieties, including analogs of pyruvate and α-ketoglutarate, which can bind cyanide through cyanohydrin formation; and (3) additional classes of compounds that can directly react with cyanide, such as (i) *N*-alkoxy and *N*-alkylthio heterocycles, and (ii) phthalocyanines and porphyrins. During this report period we prepared examples of all compound types just described. The 33 new compounds submitted this period were distributed among these compound classes as follows: sulfur-rich species, 12; polycarbonyl compounds, 13; nitrogenous heterocycles, 1; and metal complexes, 7. Some of these compounds contained multiple functionality that could react with cyanide. One of the sulfur compounds was prepared at the request of the CO and was a re-submission of an additional quantity of a previously submitted sample which had displayed positive biological results during screening (SoRI 7638; WR 268831). We have received biological testing data for 20 compounds during this same period, and now have demonstrated activity in three of our four primary target classes (no phthalocyanines have been tested for efficacy at this point). Of these 20 screened compounds, the *S*-sulfo derivative of cysteine (SoRI 7913; WR000125AC) was found to have potential as an improved pretreatment for NaCN poisoning. This brings to 5 the total number of actives designed as a part of this program, with many additional possibilities as yet unscreened. These results were used to shape our planned synthetic program of our pending, renewal application.

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ABSTRACT

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FOREWORD

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PI – Signature James R. Ogden DATE May 27, 1993

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I. INTRODUCTION

This report documents our efforts during year 3 (9 March 1992 — 8 March 1993), the final year on Contract No. DAMD17-90-C-0011, to identify new and improved prophylactic agents against the toxicity of cyanide. The synthetic effort encompassed the three areas described in the previous annual report, the detailed rationale for which is fully delineated in the original proposal (Southern Research Institute Proposal No. 88-483; USAMRDC Proposal Log No. 88321006): (i) polysulfides and other sulfur-rich compounds which can mediate cyanide detoxification through their interplay with rhodanese and other mammalian sulfur transferase systems; (ii) polycarbonyl-containing compounds which can provide multiple sites for cyanohydrin formation, one of the key detoxification routes of pyruvate and related compounds; and (iii) heteroaromatic compounds capable of undergoing cyanation, thereby removing cyanide. We also continued our investigations into a novel class of promising prophylactic substances, metal complexes including phthalocyanines, porphyrins, and simple cobalt salts, that can sequester cyanide through complexation with the constituent metal ion.

This report compiles the synthetic procedures described in reports submitted for quarters 9-12 of this contract. We have also colligated structures of all compounds supplied for testing with their corresponding identification numbers and, where available, biological test data. Experimental procedures outlining the syntheses are provided following each section.

The following instrumentation methods and procedures were used. All solvents and materials were reagent grade and were either used as received or purified as required. ^{1}H NMR and ^{13}C NMR spectra were run with a Nicolet NMC NT300 NB spectrometer operating at 300.65 Mhz with tetramethylsilane as an internal reference. Chemical shifts (δ) for multiplets were measured from the appropriate centers. The mass spectral data were obtained from a Varian MAT 311A mass spectrometer in fast atom bombardment (FAB) or electron-impact (EI) mode (direct probe temperature 20 °C), as indicated. Infrared data were obtained with a Nicolet 10-MX spectrometer. In most cases, only strong or medium peaks in the 1800-600 cm^{-1} range were reported. UV absorption spectra were determined in the appropriate solutions [pH 1 (0.1 *N* HCl), pH 7 buffer, and pH 13 (0.1 *N* NaOH)] with either a Cary 17 spectrometer or a Perkin-Elmer Model Lambda 9 UV/VIS/NIR spectrophotometer. Melting point data was obtained with a Mel-Temp Capillary Melting Point apparatus, and all melting points are uncorrected. Elemental analysis data were obtained from either an in-house Perkin Elmer Model 240 Elemental Analyzer or from Atlantic Microlab of Atlanta, Georgia.

II. NITROGENOUS AROMATIC HETEROCYCLES.

Only a single example of this compound class was submitted for biological evaluation this report period, and the physical properties of this agent (1) are presented in Table 1. Our rationale for the preparation and testing of this class of compounds was based upon the recent literature report[1] of the reaction of *N*-vinylpyrazolium salts with cyanide ion *in vitro*, and our desire to establish the potential utility of these compounds with regard to cyanide toxicity *in vivo*. The synthesis of this compound followed that in the literature, and is shown in Eq. 1.

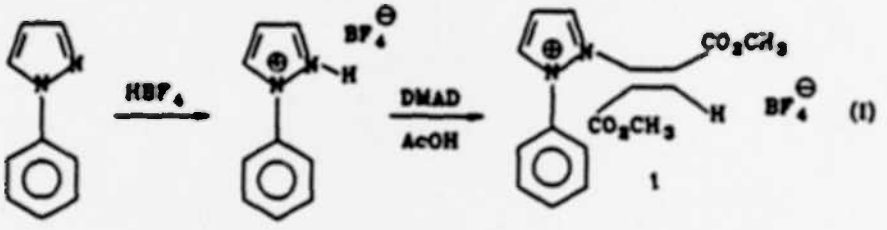


TABLE 1. NITROGENOUS HETEROCYCLES

Structure No.	Yield, %	M.P., °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found		
				%C	%H	%N
1	33	135-136	$C_{15}H_{15}N_2O_4BF_4$ (374.10)	48.16 48.06	4.04 3.96	7.49 7.41

EXPERIMENTAL SECTION FOR PART II.

Synthesis of 1-Phenyl-2-(1,2-dicarbomethoxy)vinylpyrazolium tetrafluoroborate.

1-Phenyl-2-(1,2-dicarbomethoxy)vinylpyrazolium Tetrafluoroborate.

SoRI 8605.

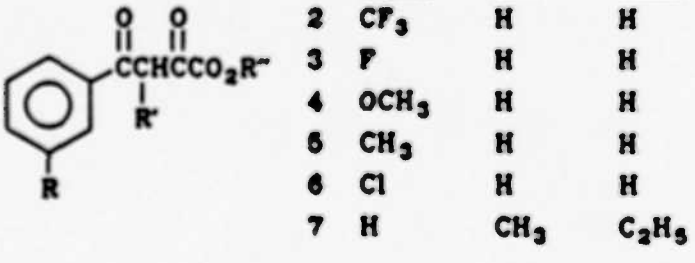
Step 1. A solution of 35 mmole of pyrazole in 40 mL of ethanol was added with stirring to 3.74 g of 48% tetrafluoroboric acid. Stirring was continued for 1 h and then solvent was evaporated under reduced pressure, yielding a viscous, oily residue. Five mL of ethyl acetate was added and the oil then allowed to cool for 2 h at 0 °C. A white solid product crystallized, which was dried under reduced pressure to obtain the pure material, m.p. 95 °C. Yield 65%.

Step 2. Equimolar portions of 1-phenylpyrazolium tetrafluoroborate (3.4 g) and dimethylacetylene dicarboxylate (2.08 g) were dissolved in acetic acid (20 mL) and refluxed for 4h. Solvent was removed under reduced pressure. A yellow-orange, viscous liquid was obtained, to which ethyl acetate (5-10 mL) was added. Upon cooling (0 °C) the product crystallized. The solid was filtered, washed with ethyl acetate, and dried under reduced pressure to obtain the pure compound. Yield 51%, m.p. 135-135 °C. *Anal.* calcd for $C_{13}H_{13}O_6N_2BF_4$: C, 48.16; H, 4.04; N, 7.49. Found: C, 48.06; H, 3.96; N, 7.41. MS $(M + 1)^+$ 287, $(M - 1)^-$ 285.

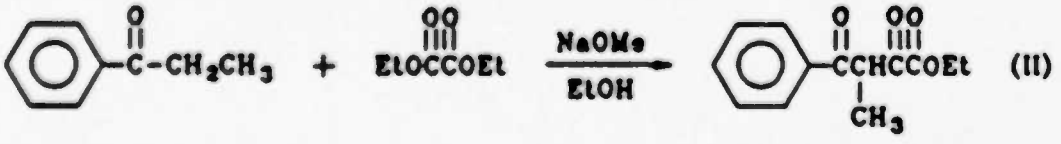
III. POLYCARBONYL COMPOUNDS

A. Derivatives of 4-Phenyl-2,4-dioxobutyric Acid.

Our rationale for preparing polycarbonyl compounds as cyanide ion trans i. based upon the stability and facile formation of cyanohydrin adducts. During the past year we have continued our exploration of substituted phenylbutyrates resulting from the condensation of the corresponding substituted acetophenone with diethyloxalate.[3,3] The structures of the six additional examples of this class that were submitted for screening this period are illustrated below (2-7). The carboxylates 2-6 were prepared by hydrolysis of the corresponding ethyl esters, compounds that were described and submitted last year. The remaining compound 7 was prepared analogously by condensation of propiophenone with diethyl oxalate (Eq. II). The physical properties of these compounds are summarized in Table 2.



	R	R'	R''
2	CF_3	H	H
3	F	H	H
4	OCH_3	H	H
5	CH_3	H	H
6	Cl	H	H
7	H	CH_3	C_2H_5

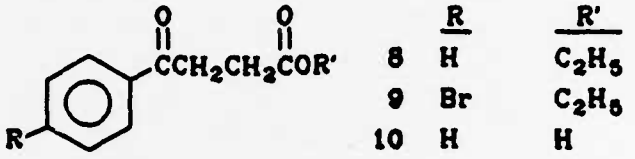


(II)

B. Derivatives of 4-Phenyl-4-oxobutyric Acid.

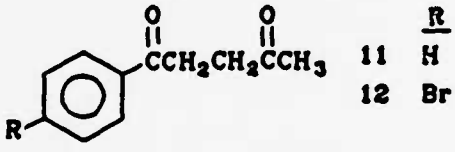
As a second class of carbonyl-containing compound capable of cyanide detoxification, we chose to prepare the three phenylbutyrates shown below (8-10). The synthesis of the two esters was based upon

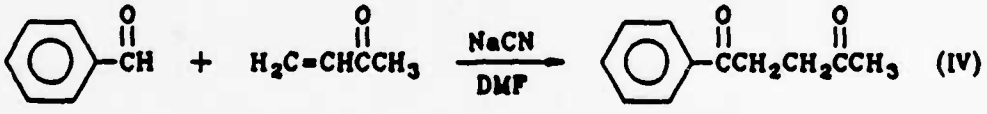
literature methods,[4] beginning with a (possibly substituted) benzaldehyde which is then treated with an α,β-unsaturated carbonyl derivative in the presence of sodium cyanide (Eq. III). The carboxylate 10 was a commercial sample (Aldrich Chemical Co., Milwaukee, WI). Table 3 summarizes the data obtained for these compounds.



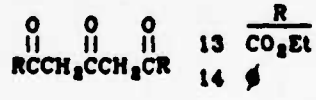
C. Miscellaneous Carbonyl Derivatives.

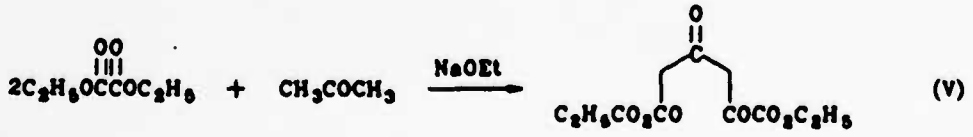
Four additional carbonyl- or polycarbonyl-containing compounds were prepared and submitted during this report period, belonging to a variety of structural types. Compounds 11 and 12 were prepared in a similar fashion to 8 and 9 just discussed, employing methyl vinyl ketone in the condensation in place of ethyl acrylate (Eq. IV).[4]





The triketones 13 and 14 were also submitted; these derivatives were prepared through the base-catalyzed condensations of methyl ketone precursors as depicted in Eqs. V and VI, respectively.[5,6]





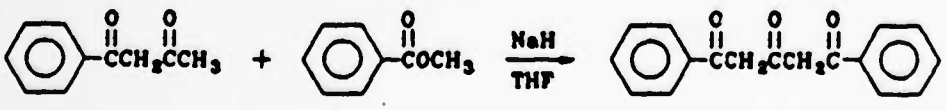


Table 4 summarizes the physical properties of these four miscellaneous carbonyl compounds.

TABLE 2. 4-PHENYL-2,4-DIOXOBUTYRATES

Structure No.	Yield, %	M.P., °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found	
				%C	%H
2	86	131-132	$C_{11}H_7O_4F_3$ (260.17)	50.78 50.72	2.71 2.49
3	88	129-132	$C_{10}H_7O_4F \cdot H_2O$ (228.18)	52.63 52.52	3.95 3.85
4	87	139-142	$C_{11}H_{10}O_5$ (222.19)	59.46 59.12	4.50 4.41
5	90	122-125	$C_{11}H_{10}O_4 \cdot H_2O$ (207.99)	63.52 63.41	4.91 4.96
6	88	145-148	$C_{10}H_9O_4Cl \cdot 0.3H_2O$ (232.02)	51.76 51.64	3.30 3.26
7	13	Liquid	$C_{13}H_{14}O \cdot 0.1H_2O$ (236.06)	66.15 66.18	6.06 5.94

TABLE 3. 4-PHENYL-4-OXOBUTYRATES

Structure No.	Yield, %	M.P., °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found	
				%C	%H
8	13	Oil	$C_{12}H_{14}O_3$ (206.23)	69.90 70.07	6.80 6.74
9	46	54-57	$C_{12}H_{13}O_3Br$ (285.12)	50.51 50.59	4.56 4.65
10	Purchased (Aldrich)	117-119	$C_{10}H_{10}O_3 \cdot 0.1H_2O$ (180.0)	66.73 66.40	5.72 5.52

TABLE 4. MISCELLANEOUS POLYCARBONYL DERIVATIVES					
Structure No.	Yield, %	M.P., °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found %C	Elemental Analyses Calcd Found %H
11	68	Oil	$C_{11}H_{12}O_2$ (176.21)	75.00 74.67	6.82 7.09
12	49	78-81	$C_{11}H_{11}O_2Br$ (255.10)	51.76 51.72	4.31 4.28
13	52	98-100	$C_{11}H_{14}O_7$ (258.22)	51.16 51.13	5.46 5.49
14	72	105-108	$C_{17}H_{14}O_3$ (266.30)	76.68 76.42	5.30 5.17

EXPERIMENTAL SECTION FOR PART III.

General Procedure for the Preparation of 4-Phenyl-2,4-dioxobutyrate Esters.

Freshly cut Na (1.2 g, 0.0521 g-atom) was added to EtOH (100-mL) under a nitrogen atmosphere, in a 500-ml, 3-neck flask equipped with a mechanical stirrer, a ground glass stopper, and a gas inlet tube. The mixture was stirred until the Na had completely dissolved, then equimolar amounts (0.05 mole each) of diethyl oxalate and the appropriate (possibly substituted) acetophenone were added. The reaction mixture was stirred for 3 h, resulting in the formation of a thick slurry. If the thickness of the slurry interfered with stirring, more EtOH was added. The slurry was suction filtered and washed with anhydrous EtOH until the wash solvent was colorless and the salt relatively dry. The salt was then added to H_2O, and the resulting suspension was acidified to pH 5 by the dropwise addition of glacial AcOH with stirring. The resulting lighter-colored solid was filtered and dried *in vacuo*. When required, the compounds were further purified by adding to H_2O, reacidifying with AcOH to pH 3, and drying *in vacuo*.

4-(3-Trifluoromethylphenyl)-2,4-dioxobutyric Acid. Yield, 86%; Mp 131-132 °C; MS (FAB) *m/e* 261 (M + 1); *Anal.* Calcd. for $C_{11}H_7O_4F_3$: C, 50.78; H, 2.71. Found: C, 50.72; H, 2.49.

4-(3-Fluoromethylphenyl)-2,4-dioxobutyric Acid. Yield, 88 %; Mp 129-132 °C; MS (FAB) *m/e* 211 (M + 1); *Anal.* Calcd. for $C_{10}H_7O_4F\ H_2O$: C, 52.63; H, 3.95. Found: C, 52.52; H, 3.85.

4-(3-Methoxyphenyl)-2,4-dioxobutyric Acid. Yield, 87%; Mp 139-142 °C; MS (FAB) *m/e* 223 (M + 1); *Anal.* Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.50. Found: C, 59.12; H, 4.41.

4-(3-Methylphenyl)-2,4-dioxobutyric Acid. Yield, 90%; Mp 122-125 °C; MS (FAB) *m/e* 207 (M + 1); *Anal.* Calcd. for $C_{11}H_{10}O_4 \cdot H_2O$: C, 63.52; H, 4.91. Found: C, 63.41; H, 4.96.

4-(3-Chlorophenyl)-2,4-dioxobutyric Acid. Yield, 88%; Mp 145-148 °C; MS (FAB) *m/e* 227 (M + 1); *Anal.* Calcd. for $C_{10}H_9O_4Cl \cdot 0.3H_2O$: C, 51.76; H, 3.30. Found: C, 51.64; H, 3.26.

Synthesis of Ethyl 3-Methyl-4-phenyl-2,4-dioxobutyrate.

Sodium methoxide (3.81 g, 70.6 mmol) was dissolved with stirring in 60 mL absolute EtOH. A solution of propiophenone (9 g, 67.06 mmol) in 30 mL EtOH was added dropwise over 1 h. The reaction mixture was stirred 1 h before a solution of ethyl oxalate (11.8 g, 80.8 mmol) in 20 mL EtOH was added dropwise over 20 min. The reaction mixture became cloudy and developed a bright yellow color during the addition. After 2 h of stirring at room temperature, the solution was evaporated to a yellow gum. The gum was treated with ice and water then acidified with conc. HCl. The reaction mixture was extracted with two portions of ether (300 mL, 100 mL). Extract and washings were pooled, washed with H_2O containing 2 mL sat. $NaHCO_3$ solution, and then with saturated NaCl solution. The extract was dried, filtered and evaporated. The crude product was purified by flash chromatography using approximately 1200 g of silica gel. The column was developed with 20:1 hexane-ethyl acetate (HE) and the product was eluted with 9:1 HE. The product contained a small impurity and so was rechromatographed (300 g siiica). Yield, 2.1 g; MS (FAB) *m/e* 235 (M + H); IR (KBr) 1751, 1731, 1673, 1450, 1291, 1269, 1248, 1208, 1112, 1040, 708 cm^{-1}; ^1H NMR ($CDCl_3$) 1.29 (t, 3H, CH_2CH_3), 1.47 (d, 3H, $CHCH_3$), 4.27 (q, 2H, CH_2CH_3), 5.05 (q, 1H, $CHCH_3$), 7.51, 7.62, 7.99 (3 m, 5H, phenyl). *Anal.* calcd for $C_{13}H_{14}O_4 \cdot 0.1H_2O$: C, 66.15; H, 6.06. Found: C, 66.18; H, 5.94.

General Procedure for Synthesis of 4-Phenyl-4-oxobutyrate Esters.

A solution of the appropriately substituted benzaldehyde (0.05 mol) in anhydrous DMF (50 mL) was added dropwise to a stirred mixture of sodium cyanide (0.025 mol) in DMF (50 mL) at 35 °C under nitrogen. After 5 min, a solution of ethyl acrylate (0.0375 mol) in DMF (50 mL) was added over a 20 min period, with the temperature maintained at 35 °C. Stirring was continued for 3 hr. The solution was then treated with two volumes of H_2O. After repeated extractions with $CHCl_3$, the pooled extracts were washed with 3*N* HCl, saturated $NaHCO_3$ solution, and finally with H_2O. After removal of the solvent the residue was purified by column chromatography.

Ethyl 4-(4-bromophenyl)-4-oxobutyrate. MS (FAB) *m/e* 285 (M + 1); Mp 54-57 °C; IR (KBr) 2985.5, 2979.1, 1729.4, 1670.8, 1583.4, 1423.0, 1400.3, 1320.6, 1305.6, 1185.8, 1176.6, 1069.1, 989.33, 768.72

cm^{-1}. *Anal.* calcd for $C_{12}H_{13}O_3Br$: C, 50.51; H, 4.56. Found: C, 50.69; H, 4.65.

Ethyl 4-phenyl-4-oxobutyrate. MS (FAB) *m/e* 207 (M + 1); IR (KBr) 3063.5, 2984.8, 2250.1, 1734.4, 1688.5, 1449.1, 1375.4, 1364.4, 1349.2, 1263.7, 1244.7, 1218.7, 1179.4, 1166.8, 749.71, 691.43 cm^{-1}. *Anal.* calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 70.07; H, 6.74.

General Procedure for Synthesis of 1-Phenyl-1,4-pentanediones.

A solution of the appropriate substituted benzaldehyde (0.1 mol) in anhydrous DMF (50 mL) was added dropwise to a stirred mixture of sodium cyanide (0.01 mol) in DMF (50 mL) at 35 °C under nitrogen. After stirring 5 min, a solution of freshly distilled methyl vinyl ketone (0.048 mol) in DMF (50 mL) was added over a 20 min period, with the temperature maintained at 35 °C. Stirring was continued for 1 h. The reaction mixture was then treated with two volumes of H_2O. After repeated extractions with $CHCl_3$, the combined extracts were washed with 3*N* HCl, saturated $NaHCO_3$ solution, and finally with H_2O. After removal of the solvent, the residue was vacuum distilled and further purified by column chromatography.

1-Phenyl-1,4-pentanedione. MS (FAB) *m/e* 177 (M + 1); IR (KBr) 1710.0, 1686.0, 1596.6, 1448.9, 1398.9, 1359.9, 1242.7, 1212.5, 1163.1, 1001.8, 746.13, 691.15, 349.11 cm^{-1}; *Anal.* calcd for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 74.67; H, 7.09.

1-(4-Bromophenyl)-1,4-pentanedione. MS (FAB) *m/e* 255 (M + 1); Mp 78-81 °C; IR (KBr) 1707.6, 1677.4, 1585.6, 1567.3, 1408.3, 140.01, 1389.8, 1352.8, 1315.8, 1209.9, 1070.0, 992.41, 847.90, 826.99 cm^{-1}; *Anal.* calc for $C_{11}H_{11}O_2Br$: C, 51.76; H, 4.31. Found: C, 51.72; H, 4.28.

Procedure for the preparation of diethyl-2,4,6-trioxoheptanedioate.

Freshly cut Na (4.6 g, 0.2 g-atom) was added to absolute ethanol (100 mL) under nitrogen. The mixture was stirred until the Na had completely dissolved. Approximately one-half of the sodium ethoxide solution was poured into a screw-top Erlenmeyer and kept at 60 °C. 5.8 g (0.1 mole) of acetone mixed with 15 g (0.103 mole) diethyl oxalate was added in one portion to the stirred sodium ethoxide solution at room temperature, resulting in a thick yellow slurry. The heated sodium ethoxide solution was then poured into the slurry, together with 16 g (0.11 mole) diethyl oxalate, the two streams being allowed to mix as they flowed into the flask. The reaction was allowed to stir at room temperature for 45 min. The flask was then equipped with a distillation condenser and heated in an oil bath until approximately 25 mL EtOH had distilled. The flask was then allowed to cool to room temperature. The slurry was poured into a large beaker over 80 g cracked ice, then acidified with 30 mL concentrated HCl. The mixture was stirred until the ice had melted

and the resulting yellow precipitate was collected by filtration washed several times with H_2O, and dried *in vacuo*.

Diethyl-2,4,6-trioxoheptanedioate. Yield, 52%; MS (FAB) *m/e* 259 (M + 1); IR (KBr) 3106.4, 2982.9, 1732.9, 1644.2, 1634.5, 1406.1, 1388.2, 1370.9, 1337.6, 1277.2, 1266.2, 1136.6, 1122.1, 1116.1, 1109.3, 1030.8, 878.22, 869.34, 820.30, 783.36, 716.09, 613.54 cm^{-1}; *Anal.* calcd. for: $C_{11}H_{14}O_7$. C, 51.16; H, 5.47. Found: C, 51.13; H, 5.49.

1,5-Diphenyl-1,3,5-pentanetrione.

A well stirred suspension of NaH (4.8 g, 0.2 mol; 60% suspension in mineral oil, 8 g) in 100 mL dry THF under argon was heated at gentle reflux and treated with a solution of benzoylacetone (6.5 g, 0.04 mol) and methylbenzoate (8.2 g, 0.06 mol) in 100 mL THF over 1 1/2 h. After a further 1 h reflux, the reaction was checked by TLC. Benzoylacetone remained so 1 mL additional methylbenzoate was added, followed by 2 h reflux. The reaction mixture was cooled and stored at room temperature overnight, then concentrated to a small volume at reduced pressure and taken up in ~200 mL ether. The ether solution was treated with ~200 mL H_2O (initially dropwise-vigorous). The organic layer was separated, washed with 100 mL H_2O, then 100 mL 1% NaOH, and pooled the aqueous extracts back washed with 150 mL ether. The aqueous phase was chilled in ice bath, ice added to the solution, which has then acidified with concentrated HCl (30 mL). The product, which crystallized, was collected; yield 8.7 g (82%). One recrystallization from hot EtOH yielded 6.8 g (72%). M.p. 105-108 °C shining yellow platelets. MS (FAB) *m/e* 267 $(M + H)^+$; 147 (M - $\emptyset COCH_2$); IR (KBr) 1603, 1595, 1567, 1538, 1493, 1450, 1378, 1280, 1163, 1157, 895, 775, 690, 685 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of ketone, enol isomers) δ 14.75 (s, 1-2, enol-OH), 7.4-7.9 (2m, 10, aromatic H), 6.31 (s, 1, C(OH)=C*H*C(O)), 6.02 (s, 2, enol; CH), 4.11 (s, 2, CH_2). *Anal.* calcd. for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.42; H, 5.17.

IV. METAL COMPLEXES

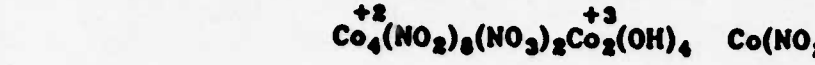
As discussed in detail in Quarterly Reports 7 and 11, we have embarked upon a synthetic program to explore the utility of metal complexes, including porphyrins, phthalocyanines, and inorganic cobalt species, for cyanide antagonism. Briefly, our premise for this approach is that the toxicity of metal ions, which have a high affinity for cyanide and effectively sequester it *in vitro*, can be reduced sufficiently if suitable water soluble complexes can be prepared. Thus, simple EDTA complexes of cobalt are already employed as cyanide antidotes in several countries, reinforcing our belief that further investigation of this concept is warranted.

After consultation with the Contract Officer, we submitted four cobalt salts (15-18) based upon our belief that the combination of cobalt with counterions that might also detoxify cyanide, such as nitrite or thiosulfate, might be doubly expedient. One of the submitted compounds, SRI 8622, was a commercial product purchased from Aldrich Chemical Co., Milwaukee, WI.

This report period, we also completed our brief survey of phthalocyanine and similar complexes, preparing the three additional systems depicted below (19-21); unfortunately, no biological data has been received for any of our metal complexes, so further synthetic activity in this area was suspended. The physical properties and structures of these compounds are presented in Table 5 and the following page.

TABLE 5. METAL COMPLEXES

Structure No.	Yield, %	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found %C	%H	%N
15	--	Remarks: This compound has not been characterized. The literature procedure was followed and we assume the product to be as described.			
16	--	Remarks: This compound has not been characterized. The literature procedure was followed and we assume the product to be as described.			
17 (Commercial Sample)	--	Remarks: This compound has not been characterized. The literature procedure was followed and we assume the product to be as described.			
18	87	Remarks: This compound has not been characterized. The literature procedure was followed and we assume the product to be as described.			
19	--	$C_{32}H_{12}N_8O_{12}S_4Na_4Ni \cdot 4H_2O$ (1,051.45)	36.55 36.17	1.91 1.99	10.65 11.63
20	--	$C_{32}H_{12}N_8O_{12}S_4Na_4Mn \cdot 6H_2O$ (1,083.74)	36.20 36.00	2.37 2.00	10.45 10.45
21	--	$C_{44}H_{28}N_8O_{12}Mn \cdot 4.5H_2O$ (996.73)	49.43 49.63	3.48 3.20	5.23 4.87



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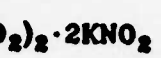

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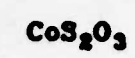

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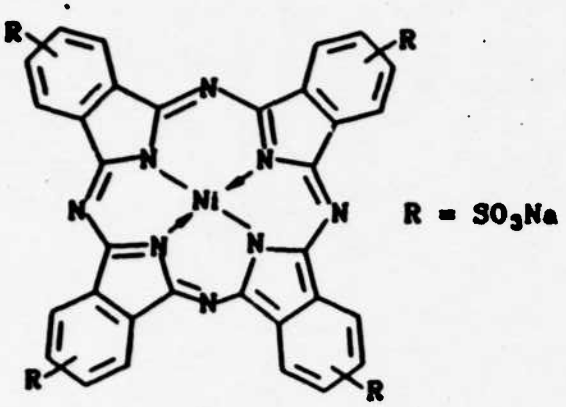

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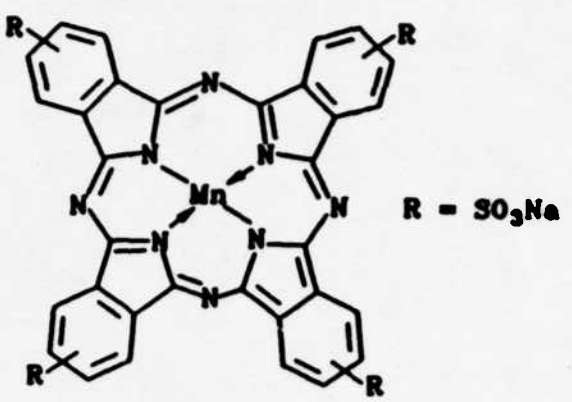

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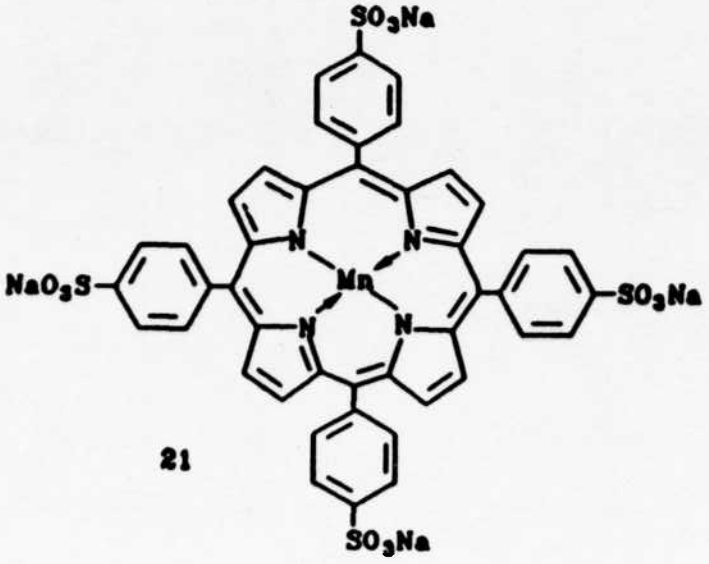

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EXPERIMENTAL SECTION FOR PART IV.

Potassium Cobaltous Tetranitrite.[7]

$$CoCl_2 + KNO_2 \longrightarrow Co(NO_2)_2 \cdot 2KNO_2 \cdot H_2O$$

SoRI 8621.

The reaction described by Remy was repeated as follows:

Cobaltous(II) chloride (5 g, 38.5 mmol) was dissolved in 75 mL H_2O. The KNO_2 (13.1 g, 0.15 mol) dissolved in 25 mL H_2O was added to the reaction solution with stirring. The mixture became turbid, and after standing at room temperature 20 min was filtered to provide a clear solution. Addition of some ethanol facilitated the formation of a yellow precipitate, which was collected, washed with additional ethanol, and dried *in vacuo* over phosphorus pentoxide. Yield, 7.9 g; IR (KBr) 1395, 1334, 829 cm^{-1}.

Hydroxycobaltoushydroxycobaltinitratenitrite.[8]

$$HNO_3 + As_2O_3 \longrightarrow N_2O_3\uparrow \xrightarrow[H_2O]{CoCO_3} Co^{+2}_4Co^{+3}_2(NO_2)_8(NO_3)_2(OH)_4 \cdot XH_2O$$

SoRI 8620.

The procedure of Suzuki was repeated. Arsenic(III) oxide (30 g) was treated dropwise with conc HNO_3. As enough liquid became available the mixture was stirred and warmed to 50-55 °C and a slow stream of argon was used to facilitate the generation and transfer of dinitrogen trioxide; this gas in turn was bubbled into a stirred aqueous suspension of $CoCO_3$ until it almost completely dissolved. The insoluble $CoCO_3$ was removed by filtration and the filtrate was evaporated *in vacuo* below 30 °C. Yield, 4.0 g; IR (KBr) 1389, 1356 cm^{-1}.

Cobalt(II) Thiosulfate.[9]

$$CoSO_4 + BaS_2O_3 \xrightarrow[H_2O]{} CoS_2O_3 + BaSO_4\downarrow$$

SoRI 8623.

A filtered solution of cobalt sulfate (3.2 g, 18.7 mmol) in 50 mL of hot water was added to a filtered solution of barium thiosulfate (5 g, 18.7 mmol) in ~1800 mL of warm water. The mixture was stirred well and stored at 5 °C overnight. The white precipitate, which had formed immediately, was removed by filtration through a celite pad. The filtrate was evaporated to dryness *in vacuo* below 30 °C. The product was

dried *in vacuo* at room temperature over phosphorus pentoxide. Yield, 2.8 g (black to dark blue powder); IR (KBr) rounded peaks 3425, 1625, 1140, 1110, 650 cm^{-1}.

Synthesis of Tetraammoniumtetra(*p*-sulfophenyl)porphine. Tetraphenylporphine (2.0 g) was suspended in concentrated H_2SO_4 (50 mL), heated on a steam bath for 6 h, then allowed to stand at room temperature overnight. The mixture was diluted with two volumes of water. The resulting bright green precipitate was filtered and washed with acetone. The residue was transferred to a beaker and dissolved in 150 mL of methanolic ammonia; impurities were filtered out. The sulfonated porphyrin was precipitated from the filtrate with three volumes of acetone, then reprecipitated six times from methanol and acetone. The product was finally dried under reduced pressure over P_2O_5. Analysis for $C_{44}H_{30}N_8O_{12}S_4 \cdot 9H_2O$. Calcd.: C, 44.23; H, 4.17; N, 9.66. Found: C, 44.26; H, 4.18, N, 9.46.

Synthesis of tetraphenylporphyrin tetrasulfonates, tetrasodium Salts. Tetraphenylporphine (2.0 g) was suspended in concentrated H_2SO_4 in a 250 mL RB flask, equipped with a condenser and drying tube. The mixture was heated on a steam bath for 6 h and then left overnight. The viscous green mixture was diluted carefully with water (150 mL) and was allowed to cool to room temperature. The green precipitate was collected by filtration and washed with acetone. The residue was suspended in 150 mL of water with celite, and slowly neuterlized with a saturated solution of sodium carbonate until the green precipitate turned purple. The mixture was then filtered to remove celite and unreacted tetraphenylporphine. The water was removed under reduced pressure. The residue was dissolved in methanol, filtered, and the residue washed with methanol, to remove the impurities. The methanol was removed and the residue again dissolved in methanol and filtered. This procedure was repeated 4 times to generate the pure product. Analysis for $C_{44}H_{26}N_4O_{12}S_4Na_4 \cdot 12H_2O$. Calcd.: C, 42.68; H, 4.06; N, 4.52. Found: 42.65; H, 4.17; N, 4.33.

Preparation of Tetrasodium Salt of Manganese (II) and Nickel(II) tetrasulfophthalocyanine. This procedure is adapted from the method of Weber and Busch.

The monosodium salt of 4-sulfophthalic acid (0.04 mole), ammonium chloride (0.02 mole), urea (0.24 mole), ammonium molybdate (0.00015 mole), and metal acetate (0.012 mole) were ground together until homogeneous. The solid mixture was heated slowly to 180 °C. The heating was continued for 6 h, maintaining a temperature between 180-190 °C The crude solid product was ground and added to 300 mL of 1*N* HCL, saturated with sodium chloride. This step is crucial for the removal of excess metal salt from the product. The solution and accompanying undissolved material were briefly heated to boiling, cooled to

room temperature, and filtered. The resulting solid was dissolved in 200 mL of 0.1 *N* NaOH. The solution was then heated to 80 °C and insoluble impurities were immediately separated. Sodium chloride (68.0 g) was added to the solution and heated to 80 °C until ammonia evolution was complete. The product was obtained by filtration, and washed with 80% ethanol until the filtrate was chloride free. This product was refluxed in 100 mL of absolute alcohol, and the product filtered and dried over P_2O_5. Analysis for $C_{32}H_{12}N_8O_{12}S_4Na_4Mn{\cdot}6H_2O$. Calcd: C, 36.20; H, 2.37; N, 10.45. Found: C, 36.00; H, 2.00; N, 10.45.

Similarly, nickel sulfophthalocyanine was prepared. Analysis for $C_{32}H_{12}N_8O_{12}S_4Na_4Ni{\cdot}4H_2O$. Calcd: C, 36.55; H, 1.91; N, 10.65. Found: C, 36.17; H, 1.99; N, 10.63.

Preparation of Manganese(III) (4-Sulfophenyl)porphine. Manganese acetate (2.5 g) and tetra(ammonium sulfophenyl)porphine (1.0 g) were dissolved in 80 mL of water and heated at 80 °C for 24 h. After cooling, the solution was evaporated to ~20 mL and passed through a Dowex 50-WX8 cation exchange column. The eluate was evaporated to dryness, dissolved in ethanol, and re-evaporated under reduced pressure. The product was re-dissolved in water, and passed through G-10 sephadex to remove inorganic impurities. The material was then dried under reduced pressure over P_2O_5. Analysis for $C_{44}H_{28}N_8O_{13}Mn{\cdot}4.5H_2O$. Calcd: C, 49.43; H, 3.48; N, 5.23. Found: C, 49.63; H, 3.20; N, 4.87.

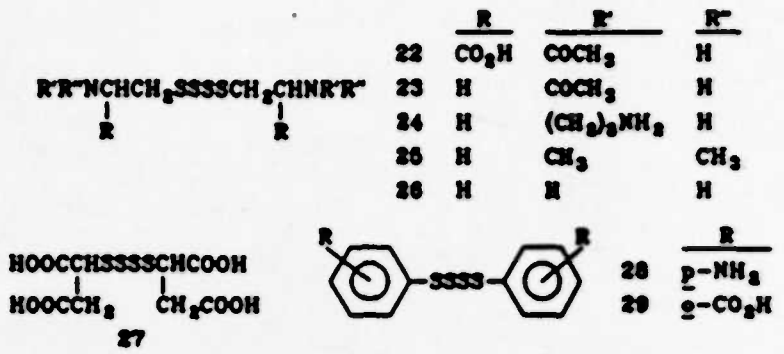
IR No. 47422, UV in water, λ_{max} 466, ϵ92.9 x 10^{-3} mol^{-1} cm^{-1}.

V. SULFUR-CONTAINING COMPOUNDS

A. Tetrasulfide Compounds.

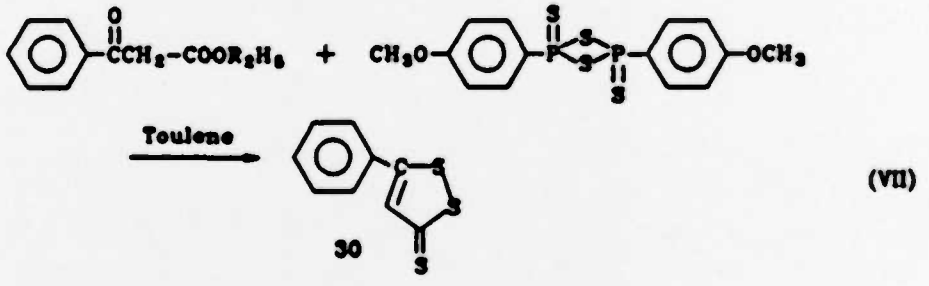
Following the favorable biological evaluation of 22 (SRI 7638; WR 268831), we began a comprehensive synthetic program targeted toward the systematic exploration of the structure-activity profile of analogous tetrasulfide derivatives. A supplemental sample of the active agent was requested by the CO for further evaluation, which was prepared, and a total of seven novel examples was also prepared and submitted. In addition, the synthesis of numerous other compounds was begun, some of which were completed but the products not yet fully purified and characterized, prior to the expiration of this project. The structures of these compounds are illustrated below. Physical data is reported in Table 6.

Compounds 23-26 share the *bis*-aminoethyl tetrasulfide motif found in the active cysteine derivative 22, the degree of substitution of the amino and methylene moieties being varied. Structures 27 and 29 were prepared to examine the requirement for the basic amino group, while 24, 25, 26, and 28 probed the necessity of the α-carboxylic acid. Finally, structures 28 and 29 examined the effect of replacement of the ethylene bridge with the planar, aromatic phenylene surrogate. Complete synthetic protocols for these compounds can be found in the experimental section.

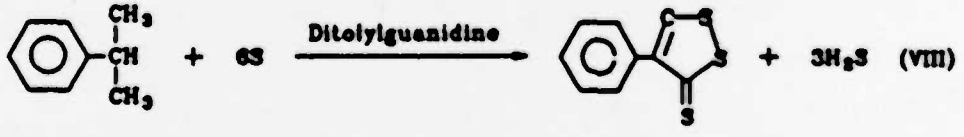


B. 3-*H*-1,2-Dithiole-3-thiones.

As discussed in last year's report, two routes were investigated for the preparation of the title compounds (Eqns. VII, VIII). The first method consistently produced reduced yields relative to method VIII. One additional example of this series (structure 30, Eqn. VII) has also been submitted. Data for this compound is summarized in Table 7.



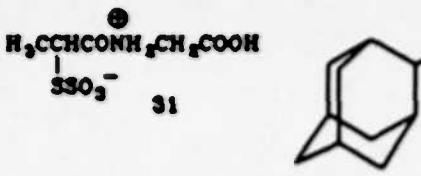
(VII)



(VIII)

C. Thiosulfates.

The biological data recently provided by Walter Reed concerning the potential of the *S*-sulfo cysteine derivative SoRI 7913 (WR 000125AC) as a pretreatment for cyanide poisoning prompted the synthesis of three additional thiosulfates for this contract. Two of these new compounds are zwitterionic amino-substituted derivatives, one (32) formed by treatment of the corresponding chloroamidine, generated *in situ*, with magnesium thiosulfate, and the other(33) by thiosulfate treatment of the corresonding aminoalkyl bromide. In addition, the *S*-sulfo derivative of glycine 31 was synthesized by treatment of the parent thiol with chlorosulfonic acid. The structures of these potential sulfane sulfur donors are summarized in the diagrams below, and their physical data follow in Table 8.



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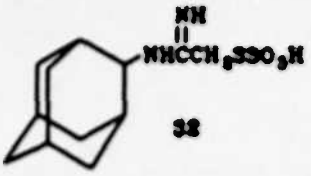

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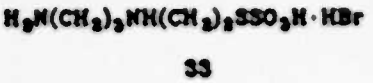

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TABLE 6. TETRASULFIDE COMPOUNDS

Structure No.	Yield, %	M.P., °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found		
				%C	%H	%N
22*	18	134-137	$C_{10}H_{16}N_2O_6S_4$ (388.52)	30.91 30.99	4.15 3.92	7.21 7.02
23	71	90-92	$C_8H_{10}O_2S_6N_2$ (373.40)	25.73 25.74	4.85 4.94	7.50 7.41
24	95	218-220	$C_{10}H_{20}N_2S_4 \cdot 4HCl$ (330.37)	25.21 25.48	6.35 6.46	11.76 11.62
25	65	172-174	$C_8H_{20}N_2S_4 \cdot HCl \cdot 5H_2O$ (317.98)	30.21 30.47	6.97 7.08	8.88 8.57
26	58	155-157	$C_6H_{12}N_2S_4 \cdot 2HCl$ (289.33)	16.60 16.85	4.88 4.96	9.68 9.82
27	35	188-192	$C_8H_{10}O_6S_4$	26.51 26.84	2.78 2.55	-- --
28	84	64-65 (dec.)	$C_{13}H_{12}N_2S_4 \cdot 2HCl \cdot H_2O$ (403.40)	35.73 35.68	4.00 3.96	6.94 6.60
29	86	--	$C_{14}H_{10}O_6S_4$	45.39 45.34	2.72 2.70	-- --

*Re-synthesis of an active, previously submitted sample.

TABLE 7. 3-*H*-1,2-DITHIOLE-3-THIONES

Structure No.	Yield, %	M.P., °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found		
				%C	%H	%N
30	Unavailable	125-126 (lit. 126)	$C_3H_2S_3$ (210.33)	51.43 51.42	2.86 2.74	-- --

TABLE 8. THIOSULFATES

Structure No.	Yield, %	M.P., °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found		
				°C	%H	%N
31	76	145-146	$C_5H_9NO_6S_2$ (243.26)	24.68 24.69	3.72 3.90	5.75 5.66
32	65	185-187	$C_{13}H_{20}N_2O_6S_2$ (304.00)	47.34 47.43	6.62 6.71	9.20 9.15
33	65	138-142	$C_6H_{14}N_2O_6S_2 \cdot HBr$ (295.22)	20.34 20.38	5.46 5.37	9.47 9.28

EXPERIMENTAL SECTION FOR PART V.

Synthesis of 2,2'-tetrathio-bis-aminoethane Dihydrochloride.

2-Aminoethanethiol (.03 mol) was dissolved in 100 mL of acetic acid. Sulfur monochloride in CH_2Cl_2 (0.12 mole) was then added dropwise under N_2 atmosphere to the stirred solution to give a white precipitate. The stirring was continued for 1/2 h at room temperature. The white solid product was collected under nitrogen, washed with acetic acid and then with diethyl ether and dried under reduced pressure over P_2O_5 at room temperature. Yield: 58%, m.p. 155-157 °C. *Anal.* Calcd. for $C_4H_{12}N_2S_2 \cdot 2HCl$. C, 15.60; H, 4.88; N, 9.68. Found: C, 16.85; H, 4.96; N, 9.82. Mass $(M + H)^+$ 217.

Synthesis of 2,2'-tetrathio-bis-*N*-Acetylcysteamine Dihydrochloride.

To a solution of *N*-acetylcysteamine (0.02 mole) in acetone (100 mL), sulfur monochloride (in CH_2Cl_2; 0.10 mL) was added dropwise under nitrogen atmosphere at room temperature. A white precipitate separated. The stirring was continued for 1 h. The product was then collected under nitrogen atmosphere, washed with acetone and diethyl ether, and finally dried under reduced pressure. Yield, 71%. M.p. 90-92 °C. *Anal.* calcd. for $C_8H_{16}O_2S_4N_2 \cdot 2HCl$. C, 25.73; H, 4.85; N, 7.50. Found C, 25.74; H, 4.49; N, 7.41. Mass $(M + H)^+$ 301.

Preparation of 2,2'-Tetrathio-bis-dimethylaminoethane Hydrochloride.

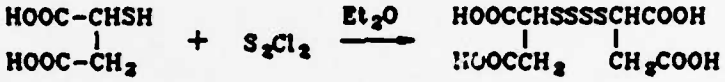
Sulfur monochloride (0.10 mole) in CH_2Cl_2 was added to a solution of dimethylamino-ethanethiol (0.02 mole) in acetone (100 mL) at 20 °C. A white precipitate appeared. The stirring was continued for 1 h. The product was collected under nitrogen, washed with acetone and ether and finally dried under reduced pressure at room temperature. Yield 65%. M.p. 172-174 °C. *Anal.* calcd for $C_8H_{20}N_2S_4HCl \cdot 1/2H_2O$. C,

30.21; H, 6.97; N, 8.88. Found: C, 30.47; H, 7.08; N, 8.57. Mass $(M + H)^+$ 273.

Preparation of *N,N'*-(tetrathiodiethylene)-1,3-propanediamine Tetrahydrochloride.

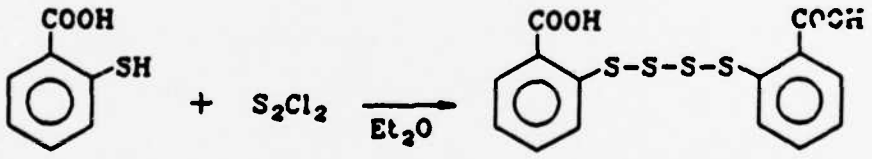
2-(3-Aminopropylamino)ethanethiol dihydrochloride (10 mmol) (obtained *via* the method reported in Report 9, page 5, step-3) was dissolved in hot acetic acid (250 mL) and then cooled to room temperature. The S_2Cl_2 (5 mmol) was added to the stirred solution. A white precipitate appeared. The stirring was continued for an additional hour. The precipitate was collected, washed with acetic acid and diethylether, and finally dried under reduced pressure. Yield 95%. M.p. 218-220 °C decomposed. *Anal.* calcd for $C_{10}H_{26}S_4N_4 \cdot 4HCl$. C, 25.21; H, 6.35; N, 11.76. Found: C, 25.48; H, 6.46; N, 11.62. Mass $(M + H)^+$ 331.

Succinic Acid, Tetrathio-bis.



A solution of mercaptosuccinic acid (6 g, 40 mmol) in 300 mL other was treated with S_2Cl_2 (20 mL, 20 mmol-1*M* solution in CH_2Cl_2) with good stirring. After ~45 min a precipitate began to form. The reaction was stirred 1 h longer, the product was collected, washed with ether, and dried *in vacuo* over phosphorus pentoxide; yield: 2.5 g (35%). M.p. 188-192 °C; MS (FAB) *m/e* 363 $(M + H)^+$; IR 1694, 1412, 1292, 1235, 1185, 935, 920 cm^{-1}; ^1H NMR (CD_3OD) δ 4.04 (q, 1, C*H*), 3.11, 2.88 (2dd, 2, CH_2). *Anal.* calcd. for $C_8H_{10}O_8S_4$: C, 26.51; H, 2.78. Found C, 26.84; H, 2.55.

2,2'-Tetrathio-*bis*-benzoic Acid.



SoR1 8624.

2-Thiosalicyclic acid (3 g, 19.5 mmol) was suspended in 200 mL Et_2O and S_2Cl_2 (9.7 mL, 9.7 mmol, 1*M* in CH_2Cl_2) was added quickly (~30 sec) with good stirring. The product rapidly began to precipitate. The mixture was stirred 30 min and then product was collected, washed with Et_2O, and dried. Yield, 3.1 g (86%) (lt yellow powder); IR 1672, 1586, 1560, 1463, 1435, 1416, 1310, 1288, 740 cm^{-1}. *Anal.* calcd for $C_{14}H_{10}O_4S_4$: C, 45.39; H, 2.72. Found: C, 45.38; H, 2.70.

4,4'-Tetrathio-*bis*-benzeneamine, Dihydrochloride.

SoRI 8599.

A solution of sulfur monochloride (1M in dichloromethane, 7.0 mL) was added slowly to a stirred solution of 4-aminothiophenol (1.98 g) in 100 mL acetone at 20 °C. A precipitate immediately appeared after the addition. Stirring was continued for 30 min. The precipitate was filtered under nitrogen and washed first with acetone then with diethyl ether, then dried under reduced pressure over P_2O_5, m.p. 64-66 °C (decomposed). Yield 84%. *Anal.* calcd for $C_{12}H_{12}N_2S_4 2HCl \cdot H_2O$: C, 35.73; H, 4.00; N, 6.94. Found: C, 35.68; H, 3.98; N, 6.6. MS $(M + H)^+$ 312.

Reaction of 3-oxoesters with *p*-methoxyphenylthionophosphine sulfide. Ethylbenzoylacetate (0.005 mole), .012 mole of Lawesson reagent, and sulfur (.01 mole) were taken up in 10 mL of anhydrous toluene and heated at 110 °C for 10 h. After cooling to room temperature, the mixture was placed on a silica gel column and the toluene was eluted with ether/light pet. ether (10:90). On a renewed elution with ether/light pet. ether (30:70) the 3*H*-1,2-dithole-3-thiones were isolated, and identified by m.p., MS, and elemental analyses. M.p., 125-126 °C. Reported, 126 °C. Mass spec. $(M + H)^+$ 211. *Anal.* calcd. for $C_9H_6S_3$. Calcd: C, 51.43; H, 2.86. Found: C, 51.42; H, 2.74.

Synthesis of *S*-[*N*-(2-Adamantyl)amidino]methyl Hydrogen Thiosulfate.

A solution of chloroacetonitrile (0.01 mole) in methanol (25 mL) was added to a stirred solution of sodium methoxide obtained from 10 mmole (0.23 g) of Na in methanol (50 mL) at 25 °C. A 30 min time was allowed for the reaction. Then a solution of 2-adamantanamine hydrochloride (0.8 mole) in methanol was added. A reddish brown color developed after 45 min, then solid magnesium thiosulfate (0.8 mole) was added in one portion with stirring. The resulting solution was stirred at room temperature for 3 h. The solid product separated, which was collected, washed successively with ethanol and diethyl ether, and finally dried under reduced pressure to give the pure product. Yield: 65%, m.p. 185-186 °C. Decomposed (Lit. 185-187 °C). *Anal.* calcd. for $C_{12}H_{20}N_2O_3S_2$; C, 47.34; H, 6.62; N, 9.20. Found C, 47.43; H, 6.71; N, 9.15. Mass spec. $(M + H)^+$ 305, $(M - H)^-$ 303.

Synthesis of *N*-[1-oxo-2-(sulfothio)propyl]glycine.

Chlorosulfonic acid (0.021 mole) was added slowly to a stirred solution of *N*-(2-mercaptopropionyl)glycine) in 100 mL of acetic acid at room temperature (25 °C). The white precipitate appeared, and stirring was continued for 1/2 h. The precipitate was collected under nitrogen atmosphere,

which was washed with acetic acid and then ether, and finally dried over P_2O_5 under reduced pressure. Yield: 76%. M.p. 145-146 °C. *Anal.* calcd for $C_5H_9NO_6S_2$. Calcd. for C, 24.68; H, 3.72; N, 5.75. Found: C, 24.20; H, 3.81; N, 5.61. Mass spec. $(M - H)^-$ 243.

***S*-2-(3-Aminopropylamino)ethyl Hydrogen Thiosulfate Hydrobromide.**

SoRI 8598.

Equimolar amounts of magnesium thiosulfate and sodium acetate (0.1 mole) in methanol (25 mL) were added to a solution of *N*-(2-bromoethyl)-1,3-propanediamine dihydrobromide (0.1 mole) in methanol. The resulting mixture was heated for 2 h at 60 °C. The solution was then concentrated to ~20 mL and kept in the refrigerator for 6-7 days. A white solid product crystallized which was washed first with 95% alcohol and then methanol, and finally dried under reduced pressure, m.p. 138-142 °C. Yield 65%. *Anal.* calcd for $C_5H_{14}N_2S_2O_3HBr$: C, 20.34; H, 5.46; N, 9.47. Found: C, 20.38; H, 5.37; N, 9.28. MS $(M + H)^+$ 215, $(M - H)^-$ 213.

VI. SUMMARY

**TABLE 9 . COMPOUNDS SUBMITTED FOR TESTING AS ANTICYANIDE AGENTS.
CONTRACT NO DAMD17-90-C-0011
1 MARCH 1992 – 1 MARCH 1993
(STRUCTURES SHOWN IN TABLE 12)**

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
268831	BM13390	7638	F828-95-30	9, (4)
008218AR	BM14093	8197	6395-152-1	9, (2)
279299AA	BM14100	8198	H099-40-2	9, (9)
279300AA	BM14119	8211	6395-147-4	9. (9)
279301AA	BM14128	8242	H099-32-1	9, (9)
279302AA	BM14137	8243	H099-36-1	9, (9)
279303AA	BM14146	8284	H099-16-2	9, (9)
255778AB	BM14155	8354	G454-79-2	9,(8)
279306AA	BM14165	8355	G454-31-2	9, (8)
279304AA	BM14173	8356	G454-72-!	9, (8)
049410AD	BM14182	8357	G454-63-1	9, (7)
279346AA	BM14717	8362	G454-63-1	10, (5,6)
279347AA	BM14726	8563	G454-95-1	10, (7)
279348AA	BM14735	8564	G454-88-2	10, (7)
166717AB	BM14744	8565	G454-85-1	10, (6)
279349AA	BM14753	8566	G454-101-3	10, (7)
279350AA	BM14762	8567	G454-97-3	10, (6)
108236AB	BM14771	8594	H099-104-1	10, (8, 10)
279351AA	BM14780	8600	F828-103-15	10, (7)
088456AD	BM14799	8601	H270-13-30	10, (10)
009720AC	BM15796	8598	G454-82-2	11, (12)
279422AA	BM15894	8599	G454-91-2	11, (12)
279414AA	BM15803	8605	G454-119-1	11, (13)
279415AA	BM15812	8609	H270-33-27	11, (8)
279411AA	BM15750	8620	H270-49-24	11, (5)
279412AA	BM15769	8621	H270-73-15	11, (5)
028134AC	BM15778	8622	H270-77-1	1!, (6)

TABLE 9. (Continued)

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
279416AA	BM15821	8623	H270-71-20	11, (6)
279417AA	BM15830	8624	H270-59-14	11, (11)
061592AD	BM15849	8625	H099-128-1	11, (10)
217431AB	BM17085	8636	H099-142-2E	12, (4)
279472AA	BM17094	8640	H099-148-2A	12, (4)
279473AA	BM17101	8646	H445-02-A	12, (4)

TABLE 10. COMPOUNDS SUBMITTED FOR TESTINC AS ANTICYANIDE AGENTS.
CONTRACT NO. DAMD17-90-C-00111
9 MARCH 1991 – 17 MARCH 1992
(ADDENDUM)

These compounds were submitted and described during the previous report period (Year 2), but the WR/bottle numbers were not available at the time of that annual report.

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
025524AE	BM12362 or 12302	8140	G395-49-1	8, (5-8)
022032AB	BM12446	8141	G395-75-1	8, (5-8)
074813AB	BM12311	8158	G395-85-1	8, (5-8)
001055AH	BM12320	8168	G395-87-1	8, (5-8)
255378AB	BM12339	8170	G454-15-1	8, (11-12)
279194AA	BM12348	8171	G076-129-1	8, (11-12)
255375AB	BM12357	8172	G454-03-03	7, (6-8)
279150AA	BM12366	8175	G395-97-1	8, (5-8)
279151AA	BM12375	8177	G395-99-2	8, (5-8)
279152AA	BM12384	8178	G395-101-2	8, (5-8)
279153AA	BM12393	8179	G395-105-2	8, (5-8)
279154AA	BM12400	8180	G395-109-3	8, (5-8)
279155AA	BM12419	8184	G395-107-4	8, (10)
279156AA	BM12428	8190	G454-37-1	8, (11-12)
279157AA	BM12437	8191	G454-39-1	8, (11-12)

TABLE 11. CANDIDATE COMPOUNDS TESTED FOR ANTICYANIDE EFFICACY DURING THIS REPORT PERIOD. 9 MARCH 1992 – 8 MARCH 1993

ICD No.	WR No.	WR Bottle No.	SoRI No.
2094	271142AA	BM09350	7849
2101	271145AA	BM09449	7872
2103	271146AA	BM09467	7903
2106	002250AB	BM09369	7864
2109	000125AC	BM09501	7913[a]
2110	271150AA	BM09510	7914
2116	271155AA	BM09583	7845
2189	001757AC	BM10326	7929
2190	272681AA	BM10335	7930
2191	102233AB	BM10344	7931
2192	001868AC	BM10353	7932
2233	276495AA	BM11029	7934
2234	276496AA	BM11038	7984
2235	276497AA	BM11047	7985
2236	276498AA	BM11056	7986
2237	276499AA	BM11065	7987
2238	276500AA	BM11083	8113
2239	276501AA	BM11092	8114
2241	001756AB	BM11118	8116
2247	000362AB	BM11074	8112

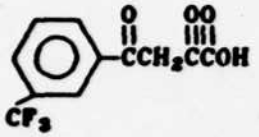
[a]Preliminary test results indicate activity.

TABLE 12. STRUCTURES OF COMPOUNDS SUBMITTED FOR TESTING AS ANTICYANIDE AGENTS.
CONTRACT NO. DAMD17-90-C-0011
9 MARCH 1992 — 19 MARCH 1993

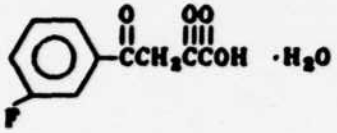
SoRI 7638

(Resynthesized at CO's request.)

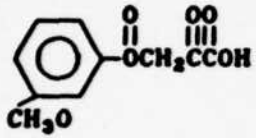
SoRI 8197



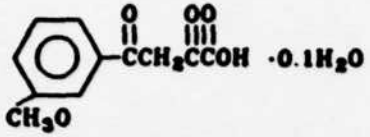
SoRI 8198



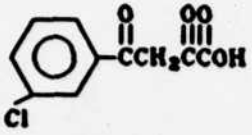
SoRI 8211



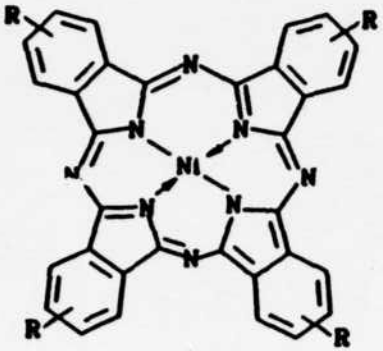
SoRI 8242



SoRI 8243

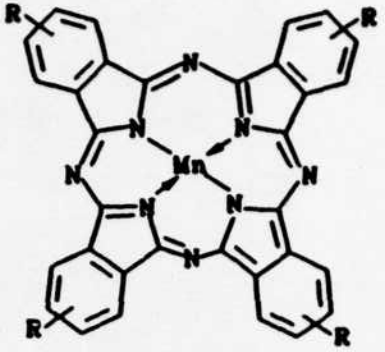


SoRI 8284



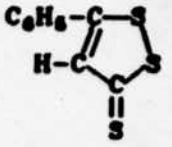
SoRI 8354

R = SO_3Na

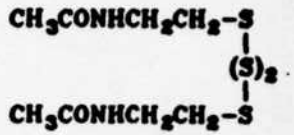


SoRI 8355

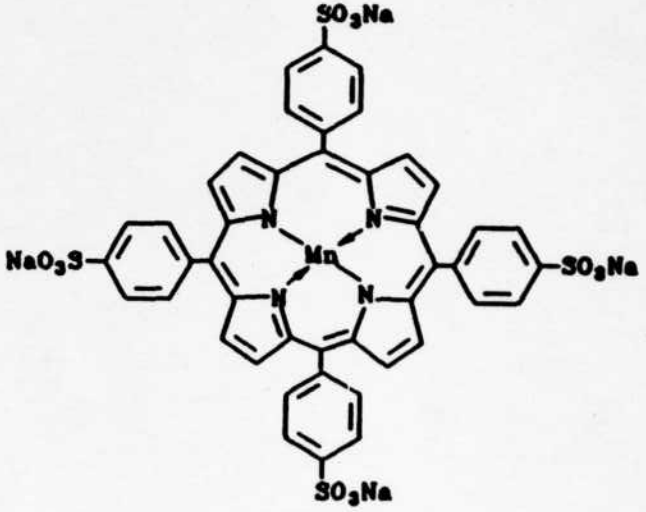
R = SO_3Na



SoRI 8357

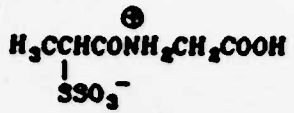


SoRI 8562



SoRI 8356

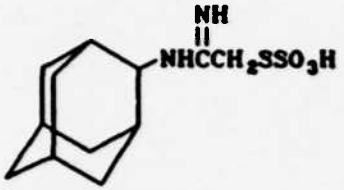
TABLE 12. (Continued)



SoRI 8563

$H_2N(CH_2)_3NH(CH_2)_2SSSS(CH_2)_2NH(CH_2)_3NH_2 \cdot 4HCl$

SoRI 8564

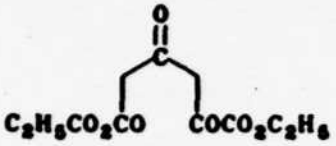


SoRI 8565

SoRI 8566

$H_2NCH_2CH_2SSSSCH_2CH_2NH_2 \cdot 2HCl$

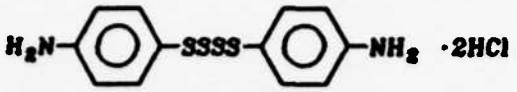
SoRI 8567



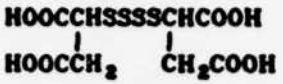
SoRI 8594

$H_2N(CH_2)_3NH(CH_2)_2SSO_3H \cdot HBr$

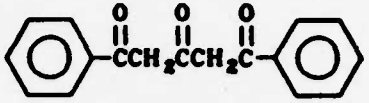
SoRI 8598



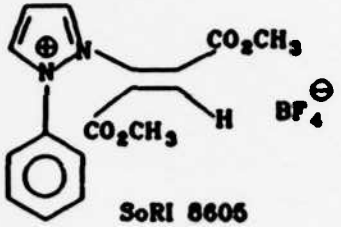
SoRI 8599



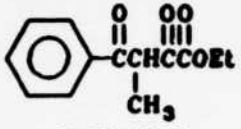
SoRI 8600



SoRI 8601



SoRI 8605



SoRI 8609

$Co_4^{+2}(NO_2)_8(NO_3)_2Co_2^{+3}(OH)_4$

SoRI 8620

$Co(NO_2)_2 \cdot 2KNO_2$

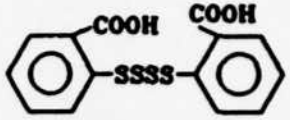
SoRI 8621

$Na_3Co(NO_2)_6$

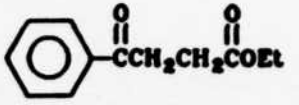
SoRI 8622

CoS_2O_3

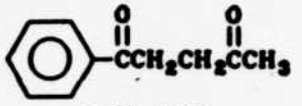
SoRI 8623



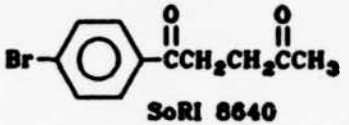
SoRI 8624



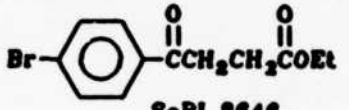
SoRI 8625



SoRI 8636



SoRI 8640



SoRI 8646

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